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## ORIGINAL ARTICLE

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## Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. A randomized, double-blind, placebo-controlled trial. The HA-1A Sepsis Study Group

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### Abstract

**BACKGROUND.** HA-1A is a human monoclonal IgM antibody that binds specifically to the lipid A domain of endotoxin and prevents death in laboratory animals with gram-negative bacteremia and endotoxemia. **METHODS.** To evaluate the efficacy and safety of HA-1A, we conducted a randomized, double-blind trial in patients with sepsis and a presumed diagnosis of gram-negative infection. The patients received either a single 100-mg intravenous dose of HA-1A (in 3.5 g of albumin) or placebo (3.5 g of albumin). Other interventions, including the administration of antibiotics and fluids, were not affected by the study protocol. **RESULTS.** Of 543 patients with sepsis who were treated, 200 (37 percent) had gram-negative bacteremia as proved by blood culture. For the patients with gram-negative bacteremia followed to death or day 28, there were 45 deaths among the 92 recipients of placebo (49 percent) and 32 deaths among the 105 recipients of HA-1A (30 percent;  $P = 0.014$ ). For the patients with gram-negative bacteremia and shock at entry, there were 27 deaths among the 47 recipients of placebo (57 percent) and 18 deaths among the 54 recipients of HA-1A (33 percent;  $P = 0.017$ ). Analyses that stratified according to the severity of illness at entry showed improved survival with HA-1A treatment in both severely ill and less severely ill patients. Of the 196 patients with gram-negative bacteremia who were followed to hospital discharge or death, 45 of the 93 given placebo (48 percent) were discharged alive, as compared with 65 of the 103 treated with HA-1A (63 percent;  $P = 0.038$ ). No benefit of treatment with HA-1A was demonstrated in the 343 patients with sepsis who did not prove to have gram-negative bacteremia. For all 543 patients with sepsis who were treated, the mortality rate was 43 percent among the recipients of placebo and 39 percent among those given HA-1A ( $P = 0.24$ ). All patients tolerated HA-1A well, and no anti-HA-1A antibodies were detected. **CONCLUSIONS.** HA-1A is safe and effective for the treatment of patients with sepsis and gram-negative bacteremia.

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